

Memo to the File

NDA number: 21-526

Sequence number/date/type of submission: N(000)B2

Information to sponsor: Yes () No (x)

Sponsor and/or agent: CVT Therapeutics

Manufacturer for drug substance :

Division name: Division of Cardio-Renal Drug Products

HFD #: 110

Drug:

Trade name: Ranexa

Generic name (list alphabetically): ranolazine

Code name: RS-43285-193, RS-43285-003, CVT-303, RAN D, Ran4

Chemical name:

IUPAC: N-(2,6-dimethylphenyl)-2-(4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazinyl)acetamide

CAS¹: 1-piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-

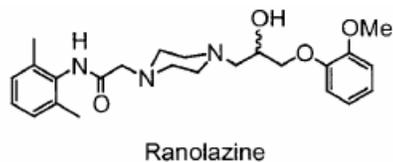
Other: (±)-4-[2-hydroxy-3-(o-methoxyphenoxy)propyl]-1-piperazineaceto-2',6'-xylidide

CAS registry number: 95635-55-5

Mole file number:

Molecular formula/molecular weight: C₂₄H₃₃N₃O₄/427.54

Structure:



Relevant INDs/NDAs/DMFs: IND 43,735

Drug class: anti-anginal

Indication: angina

Route of administration: oral

Proposed use: angina for those patients in whom all other anti-anginals are inadequate or not tolerated

The current submission was provided to try to address questions raised in the Discipline Review Letter. The sponsor has submitted the following:

Cerep 951003: In Vitro Pharmacology - Study of Several Compounds. Binding of Ranolazine, Its Enantiomers and Eleven Metabolites to the alpha1-adrenergic Receptors and Opiate Receptors. Effects of Ranolazine, Its R- and S-enantiomers on phenylephrine-induced Contraction in Isolated Rabbit Aorta.

Cerep 951006 and 951009: Binding of Ranolazine, Its Enantiomers and Eleven Metabolites to Human Serotonin 5-HT1A Receptors

CVT303.029-N: Binding of Ranolazine, Its Enantiomers and Three Metabolites (CVT -2514, CVT -2551 and CVT -3388) to the alpha-adrenergic Receptors in Rat Tissues (Addendum to Cerep 951003)

CVT303.030-N: Binding of Ranolazine, Its Enantiomers and Eleven Metabolites to the

beta-adrenergic Receptors and their Antagonism of Isoproterenol-induced Increase in cAMP

CVT303.059-P: Electrophysiologic Effects of Ranolazine on Late I_{Ca} in Isolated Canine Left Ventricular Myocytes

CVT303.061-P: Ant arrhythmic Effects of Ranolazine in a Human LQT Model: The In Vitro Guinea Pig Heart Perfused with the Proarrhythmic Sea Anemone Toxin ATX-II

CVT303.062-P: Functional Evidence of Anti-alpha Adrenergic Activity of Ranolazine in Awake Rats

CVT303.063-P: Effects of Ranolazine Enantiomers on I_{Ks}, I_{Kr}, and Late I_{Na}, and Ranolazine Metabolites on Late I_{Na}

CVT303.064-P: Functional Evidence of Anti-beta Adrenergic Activity of Ranolazine in Awake Rats

CVT303.065-P: Effects of Ranolazine on Ventricular Repolarization in Rabbit Isolated Hearts

CVT303.066-P: Effect of Ranolazine, Its R and S Enantiomers, and Eleven Metabolites on Rat Left Atrial Contractility

CVT303.067 -P: Effects of Ranolazine on Systemic Hemodynamics and Coronary Circulation in Conscious Dogs

CVT303.068-P: Electrophysiologic Effects of Ranolazine in Arterially-perfused Wedge Preparations from the Canine Left Ventricle: A Comparison Between Epicardial and Endocardial Stimulation

CVT303.069-P: Effect of Ranolazine on I_{Ks} in Isolated Canine Left Ventricle Myocytes

CVT303.070-P: Effects of Ranolazine on Isoproterenol-, Forskolin-, and Ouabain-induced Delayed Afterdepolarizations and Triggered Activity of Guinea Pig Ventricular Myocytes

MDS 1011172: Effect of the R- and the S-enantiomers of Ranolazine on the Inhibition of Neurogenic Twitch in Isolated Guinea Pig Ileum (a Serotonin 5-HT_{1A} Receptor-mediated Response)

MDS 1011220: Binding of Ranolazine, Its Enantiomers and Eleven Metabolites to the Benzothiazepine, Dihydropyridine and Phenylalkylamine-binding Sites of the L-type Calcium Channels

MDS 1033853: Effects of Ranolazine on Serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2B} Receptor-mediated Responses in Isolated Tissues

CVT303.013-R: Pharmacokinetics of Enantiomers of CVT -303 (Ranolazine), CVT -3758 (S-Enantiomer), and CVT -3759 (R-Enantiomer) in Male Beagle Dogs Following Intravenous Administration of CVT -303, CVT -3758 and CVT -3759

CVT303.014-R: Pharmacokinetics of Enantiomers of CVT -303 (Ranolazine), CVT -3758 (S-Enantiomer), and CVT -3759 (R-Enantiomer) in Male Sprague Dawley Rats Following Intravenous and Oral Administration of CVT -303, CVT -3758 and CVT -3759
CVT303.015-R: Pharmacokinetics of Enantiomers of CVT -303 (Ranolazine), CVT -3758 (S-Enantiomer), and CVT -3759 (R-Enantiomer), in Male Beagle Dogs Following Oral Administration of CVT -303, CVT -3758 and CVT -3759

Attachment 5-1: Assessing Predictors of Drug-induced Torsade de Pointes

Attachment 5-2: Ophthalmology Data

Attachment 5-3: Pathology Data

Attachment 5-4: Summary of Results. Organ Weights and Microscopic Findings for Male and Female Reproductive Organs in Individual Repeated Dose Oral Studies in Rats and Dogs

This memo is not so much a review as a statement and brief commentary on the material provided.

Cerep 951003 Binding of ranolazine, its enantiomers and eleven metabolites to the $\alpha 1$ -adrenergic receptors and opiate receptors. Sept 10, 2003: Ranolazine and the R and S enantiomers showed < 20% inhibition of specific 3H-naloxone binding to opiate receptors in membranes prepared from rat cerebral cortex. Two of the metabolites (CVT-3388 and CVT5030) showed significant binding to the opiate receptors with K_i values of 2.7 and 2.3 μM respectively. Both of these metabolites produced 68% inhibition of specific tritiated naloxone binding. Ranolazine, both enantiomers and several metabolites showed significant α -adrenergic receptor binding as summarized in the reviewer's table below.

Ki values (μM) of test compounds for α -adrenergic and opiate receptors in rat cerebral cortex

	α -adrenergic receptors	Opiate receptors
Ranolazine	1.9	n.d.
R-enantiomer	2.1	n.d.
S-enantiomer	1.7	n.d.
CVT-2514	4.9	n.d.
CVT-2551	2.6	n.d.
CVT-3388	1.5	2.7
CVT-5030	>30	2.3

n.d.= not done

Ranolazine and both enantiomers were also effective in the phenylephrine-induced contraction in rabbit aorta, supporting α -adrenergic ability.

Cerep 951006 and 951009 Summary: Binding of ranolazine, its enantiomers and eleven metabolites to human serotonin 5-HT_{1A} receptors. Sept 10, 2003

The report lists K_i values for ranolazine and its enantiomers for opiate receptors as well as 5HT_{1A} binding. These are summarized in the reviewer's table below.

	K_i value (μM) for opiate receptors	%inhibition of specific binding (10 μM)human serotonin 5HT _{1A} in mammalian cells (K_i μM)
Ranolazine	2.1	71
R-enantiomer	13.0	32
S-enantiomer	1.0	81
CVT-3248		6
CVT-2537		13

CVT-3388		52
CVT-2551		80
CVT-2514		64
CVT-2513		27
CVT-2512		13
CVT-2738		20
CVT-2535		-10
CVT-4786		12
CVT-5030		39

CVT303.029-N : Addendum to Cerep 951003, Binding of ranolazine, its enantiomers and 3 metabolites to α -adrenergic receptors. The study confirmed the previous findings that ranolazine and several of the metabolites showed α -adrenergic binding. The sponsor's table is shown below.

Table 1. IC₅₀ values (μ M) of test compounds for α -adrenergic receptors in rat tissues.

tissues (receptor subtype)	gland (α 1A)	liver (α 1B)	brain (α 1A/B)
compound	IC50 values, μ M		
Ran	13.9	34.2	19.0
Ran-R	30.4	39.6	30.8
Ran-S	8.3	27.7	14.8
CVT-3388	12.8	25.4	18.9
CVT-2514	30.2	18.9	26.5
CVT-2551	14.2	28.7	21.2

Table 2. K_i values (μ M) of test compounds for α -adrenergic receptors in rat tissues.

tissues (receptor subtype)	gland (α 1A)	liver (α 1B)	brain (α 1A/B)
compound	K _i values, μ M		
Ran	5.6	18.9	10.2
Ran-R	12.3	21.9	16.5
Ran-S	3.4	15.3	7.9
CVT-3388	5.2	14.1	10.2
CVT-2514	12.2	10.5	14.2
CVT-2551	5.7	15.9	11.4

The affinities of test compounds (i.e. K_i values) were calculated based on the Cheng Prusoff equation, $K_i = IC_{50} / (1 + (L/K_D))$, where L is the concentration of radioligand in the assay and K_D is the affinity of ³H-prazosin for α -adrenergic receptors. The K_D values for α -adrenergic receptors in rat salivary gland, rat liver and rat brain are 0.17 nM, 0.31 nM and 0.29 nM, respectively (1-4).

Electrophysiology studies:

The electrophysiology findings provided do not supersede the clinical findings of QT prolongation and cannot be extrapolated to provide human safety information

CVT303.064-P Functional evidence of anti-beta adrenergic activity of ranolazine in awake rats. July-August 2003. The study provides evidence that ranolazine has functional β -adrenergic antagonistic activity in conscious rats. Atenolol was used as a comparator compound in attempts to modify the dose-response curve of isoproterenol. A less specific β -blocker such as carvedilol might have been a more appropriate comparator. The sponsor does not show time course data for the cardiovascular effects

CVT303.067-P Effects of ranolazine on systemic hemodynamics and coronary circulation in conscious dogs. August 11, 2003-September 5, 2003. Chronically instrumented dogs were given increasing intravenous doses of ranolazine with a 30 minute interruption of infusion between each dose (bolus + infusion). The experimental protocol for each dose lasted 45 minutes with recordings of the measured parameters obtained at 0, 5,10, 15, 20, 30 and 45 minutes and blood samples collected after each recording except for 0 minutes. However, the only data presented or discussed was the 0 and 15 minute data. This “snapshot” view of the results is unhelpful and unacceptable. As reported, the study is inconclusive.

MDS 1011172 Effect of the R- and S- enantiomers of ranolazine on the inhibition of neurogenic twitch in isolated guinea pig ileum (a serotonin 5-HT_{1A} receptor-mediated response). August 28, 2003 Apparently significant agonism was seen as demonstrated by a $\geq 50\%$ decrease in field stimulated contractile responses by CVT3758 (S-enantiomer, 68% agonism at 10 μM) and CVT-3759(R-enantiomer, 157% agonism at 10 μM) at concentrations of $\geq 10\mu\text{M}$. A selective serotonin 5HT_{1A} antagonist WAY-100635 produced minimal reversal of the enantiomers effects. Was there a problem in the assay or are the effects due to factors other than serotonin antagonism? A dose response was shown in the results.

MDS1033853 Effects of ranolazine on serotonin 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2B} receptor-mediated responses in isolated tissues. Ranolazine inhibited the neurogenic twitch in isolated guinea pig ileum (a serotonin 5-HT_{1A} receptor mediated response) with an EC₅₀ value of 5.3 μM . No activity was reported for 5HT_{2A} and 5HT_{2B} receptors as measured by contraction or inhibition of agonist-induced contraction in rat aorta or stomach respectively.

MDS 1011220 Binding of ranolazine, its enantiomers and eleven metabolites to the benzothiazepine, dihydropyridine and phenylalkylamine binding sites of the L-type calcium channels. August 14, 2003 Very minimal calcium channel binding was demonstrated.

CVT303.013-R Pharmacokinetics of enantiomers of CVT-303(ranolazine), CVT-3758(S-enantiomer) and CVT-3759(R-enantiomer) in male Beagle dogs following intravenous administration of CVT-303, CVT-3758 and CVT-3759. June 4- June17, 2003

Three male dogs were used in this pharmacokinetic comparison of the enantiomers when given in the racemic mix and when given individually. The plasma analysis procedure used produced baseline resolution of the enantiomers with retention times of 9.6 (CVT-3758) and 15.5 (CVT-3759) minutes. The sponsor's results are shown below.

Pharmacokinetic parameters of the two enantiomers are summarized in the following t

Compound Dosed	CVT-303 (Racemate)		CVT-3758 (S)	CVT-3759 (R)
Dose	0.5 mg/kg total 0.25 mg/kg each enantiomer		0.5 mg/kg	0.5 mg/kg
Enantiomer	CVT-3758 (S)	CVT-3759 (R)	CVT-3758 (S)	CVT-3759 (R)
AUC _(0-t) (ng•hr/mL)	93.1±5.85	57.3±5.90	168±15.2	138±10.1
AUC _(0-∞) (ng•hr/mL)	100±7.03	67.2±6.14	180±20.0	143±11.8
CL _p (mL/min/kg)	41.7±2.91	62.4±5.75	46.8±5.42	58.4±4.98
V _{d_p} (L/kg)	1.92±0.104	2.00±0.303	2.09±0.154	2.21±0.126
t _{1/2} (hr)	0.53±0.03	0.37±0.03	0.52±0.08	0.44±0.05

Values represent mean±SD of three dogs.

There appear to be slight differences in the AUC and clearance values for the enantiomers where the S enantiomers appears in the plasma at a ratio of 1.1 to 1.7 compared to the R- enantiomers. The clearance for the R-enantiomer is slightly higher than that for the S-enantiomer. AUC for the S-enantiomer was also slightly greater than AUC for the R-enantiomer. While the results are consistent between the administration of the racemic mix and the single isomers, the sample size is small. Also, it was reported that both compounds were below the limits of detection by 1(R-enantiomer) to 2(S-enantiomer) hours after intravenous dosing. Therefore, the sampling times of 2,5,15 and 30 minutes followed by 1,2,4,6,8,10 12 and 24 hours post-dose were not optimal for characterization. The report noted that the R enantiomer was not found after intravenous dosing of the S-enantiomer and vice versa.

CVT303.014R Pharmacokinetics of enantiomers of CVT-303, CVT-3758 and CVT-3759 in male Sprague-Dawley rats following intravenous and oral administration of CVT303, CVT3758 and CVT3759. August7-18, 2003. Oral and intravenous doses of the racemic mix and the enantiomers were tested. Quantification was by the same chiral separation methods as used for the dog study. Blood samples were collected from the rats at 2.5, 5, 15.30 minutes and 1, 2, 4, 6, 8 and 24 hours after intravenous dosing and at 5, 15, 30 minutes and 1, 1.5, 2, 4, 6, 8 and 24 hours after oral dosing.

The sponsor's results are shown below.

Summary Table 1: Pharmacokinetics of CVT-3758 and CVT-3759 Following Intravenous and Oral Administration of CVT-303

Compound Dosed	CVT-303 (Racemate)		CVT-303 (Racemate)		CVT-303 (Racemate)	
	Intravenous Doses (mean \pm SD, n=3)					
Dose ^a	5 mg/kg		10 mg/kg		25 mg/kg	
Enantiomer	CVT-3758 (S)	CVT-3759 (R)	CVT-3758 (S)	CVT-3759 (R)	CVT-3758 (S)	CVT-3759 (R)
AUC _(0-∞) (ng \cdot hr/mL)	536 \pm 72.8	464 \pm 57.5	1,168 \pm 64.9	953 \pm 42.7	3,263 \pm 418	2,781 \pm 418
AUC _(0-∞) (ng \cdot hr/mL)	571 \pm 31.9	479 \pm 46.2	1,181 \pm 64.5	961 \pm 42.6	3,275 \pm 425	2,792 \pm 415
CL _p (mL/min/kg)	73.1 \pm 4.04	87.5 \pm 8.11	70.7 \pm 3.95	86.8 \pm 3.90	64.3 \pm 8.29	75.7 \pm 10.9
Vd _p (L/kg)	4.85 \pm 0.804	4.95 \pm 0.32	4.43 \pm 0.373	4.74 \pm 0.290	4.44 \pm 0.275	4.75 \pm 0.29
t _{1/2} (hr) ^d	0.76 \pm 0.09	0.66 \pm 0.056	0.72 \pm 0.06	0.63 \pm 0.01	0.80 \pm 0.07	0.73 \pm 0.09
	Oral Doses (mean \pm SD, n=4)					
Dose	5 mg/kg		20 mg/kg		50 mg/kg	
AUC _(0-∞) (ng \cdot hr/mL)	187 \pm 56.0	120 \pm 46.3	1,536 \pm 365	1,133 \pm 306	4,607 \pm 896	3,524 \pm 614
AUC _(0-∞) (ng \cdot hr/mL)	203 \pm 62.0	133 \pm 48.7	1,782 \pm 453	1,253 \pm 345	4,824 \pm 1,129	3,580 \pm 772
C _{max} (ng/mL)	120 \pm 18.7	91.5 \pm 17.4	834 \pm 195	739 \pm 184	1,933 \pm 837	1,847 \pm 869
T _{max} (hr)	0.44 \pm 0.13	0.44 \pm 0.13	0.31 \pm 0.13	0.31 \pm 0.13	0.33 \pm 0.20	0.208 \pm 0.08
F (%)	35.7 \pm 10.9	27.6 \pm 10.1	78.2 \pm 19.9	65.2 \pm 18.0	84.6 \pm 19.8	74.7 \pm 16.1

^a Values represent dose of CVT-303 (racemate). The dose of the individual enantiomers would be half.

Summary Table 2: Pharmacokinetics of CVT-3758 and CVT-3759 Following Administration of the Individual Enantiomers

Route	Intravenous (mean \pm SD, n=3)		Oral (mean \pm SD, n=4)	
Enantiomer Dosed	CVT-3758 (S)	CVT-3759 (R)	CVT-3758 (S)	CVT-3759 (R)
Dose ^a	5 mg/kg	5 mg/kg	5 mg/kg	5 mg/kg
AUC _(0-∞) (ng \cdot hr/mL)	812 \pm 36.4	876 \pm 182	400 \pm 97.7	277 \pm 110
AUC _(0-∞) (ng \cdot hr/mL)	823 \pm 42.1	895 \pm 169	457 \pm 20.5	297 \pm 115
CL _p (mL/min/kg)	101 \pm 5.1	95.7 \pm 20.2	nc ^b	nc
Vd _p (L/kg)	6.00 \pm 0.56	4.92 \pm 0.170	nc	nc
t _{1/2} (hr)	0.69 \pm 0.09	0.61 \pm 0.10	nc	nc
C _{max} (ng/mL)	nc	nc	227 \pm 97.7	199 \pm 65.0
T _{max} (hr)	nc	nc	0.438 \pm 0.24	0.25 \pm 0.00
F(%)	nc	nc	55.4 \pm 12.5	33.2 \pm 12.9

^a Values represent dose of the individual enantiomers CVT-3758 and CVT-3759.

^b nc = Not calculated.

At each dose by both routes of administration, the S-enantiomer produced non-significantly higher plasma levels than did the R-enantiomer. Clearance was also slightly higher for the R-enantiomer. Bioavailability was slightly greater for the S-enantiomer. The results are consistent with the dog study. The report noted that the R enantiomer was not found after either oral or intravenous dosing of the S-enantiomer and vice versa.

CVT303.015-R Pharmacokinetics of enantiomers of CVT-303, CVT-3758 and CVT-3759 in male Beagle dogs following oral administration of CVT-303, CVT3758 and CVT3759. August 11-August 27, 2003. Four male Beagles received oral doses of either the racemic mixture or the enantiomers of ranolazine. Blood samples were collected at 2,5, 15, and 30 minutes and at 1,2,4,6,8,10, 12 and 24 hours post-dose. The results from this study were consistent with the previous two studies. The report noted that CVT-3759 was not found in plasma after administration of CVT-3758 and vice versa.

Assessing predictors of drug-induced torsade de pointes. Accepted in Trends in Pharmacological Sciences. Noted as scheduled for publication in December 2003.

This is a preprint of a manuscript authored by the sponsor the details the sponsor's criteria for deciding pro-arrhythmic risk from preclinical studies.

Attachment 5-2: In a telecom, this reviewer expressed a concern that none of the preclinical toxicology reports included an ophthalmologist's report, nor any indication that a board certified veterinary ophthalmologist had examined any of the animals in any studies. In fact, there are recent studies where it was specified that examinations were conducted by a staff veterinarian instead of an ophthalmologist. In response to that concern, the sponsor has sent the individual animal data for the ophthalmic exams for the following studies:

AT3465: RS-43285RHT: Three month oral toxicity study in rats
AT3935: RS43285 RJT: Six month oral toxicity study in rats with one month recovery period.
AT6544: RS-43285-RKT: One year rat toxicity study
AT3440: RS-43285DHT: Three month oral toxicity study in dogs
AT4050: RS-43285DJC:six month oral toxicity study in dogs
AT6971: RS-43285 DKC: One year oral toxicity study in dogs

While the individual animal sheets are signed, there is no indication that the person signing is a qualified veterinary ophthalmologist. There is no summary of the findings, and no statement from the person conducting the examinations as to a conclusion.

Attachment 5.3 Pathology data

In the above mentioned telecom, this reviewer also noted that there was no complete summary of histopathologic findings provided for any study and that the absence of data did not mean that one could assume that there was no problem. In this attachment, the sponsor has provided material for the following studies:

AT3465: RS-43285RHT: Three month oral toxicity study in rats
AT3935: RS43285 RJT: Six month oral toxicity study in rats with one month recovery period.
AT6544: RS-43285-RKT: One year rat toxicity study
AT3440: RS-43285DHT: Three month oral toxicity study in dogs
AT4050: RS-43285DJC:six month oral toxicity study in dogs
AT6971: RS-43285 DKC: One year oral toxicity study in dogs

The material submitted does not significantly contribute to elucidation of the histopathological questions.

Summary: The material submitted does not materially change the preclinical characterization of ranolazine.